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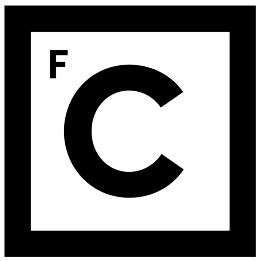

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Automatically finding tumors using structural-prior guided optical tomography

MESTRADO INTEGRADO EM ENGENHARIA BIOMÉDICA E BIOFÍSICA
PERFIL EM SINAIS E IMAGENS MÉDICAS

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“Do you realize that ‘IMPOSSIBLE’ is just a word that makes me try even harder?”

Leonardo da Vinci

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It was a real pleasure to work at the Optical Unit, and a privilege to give my contribution to Martinos Center/MGH. Therefore I would like to express my gratitude to all of those who made this thesis possible.

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ABSTRACT

Diffuse optical tomography (DOT) is a diagnostic tool that relies on functional processes for contrast. This technique provides several unique measurable parameters with the potential to enhance breast tumor sensitivity and specificity. DOT utilizes non-ionizing radiation and it is non-invasive.

Several groups have begun incorporating DOT with other imaging modalities. This approach can potentially overcome the resolution limitation problem by using spatial information provided by other imaging modalities. In this sense, a co-registered DOT with 3D X-ray mammography (also known as tomosynthesis) has been developed at Massachusetts General Hospital in order to utilize anatomical information as a structural prior. Literature reveals that the compositional-prior-guided reconstruction algorithm is sensitive to false priors on tumor location. So far, most clinical research of either standalone or multi-modal DOT breast imaging system have been focusing on characterizing known tumors. It has not been shown that, DOT based imaging methods can be used to identify the location, and type of an unknown lesion. So, the purpose of this work is the development of a computer aided detection (CAD) method to automatically identify the location and types of an unknown lesion without interference from a radiologist.

In this thesis, to reconstruct the images was used the compositional prior guided reconstruction algorithm considering 2-composition prior (adipose and fibroglandular tissues) and 3-composition prior (adipose, fibroglandular and tumor tissues), which depends of the tumor location. The tumor contrast from those results were investigated using quantitative contrast metrics. The development of the tumor contrast metrics was based on the measurements from a set of 126 breasts (66 normal and 60 abnormal) using the DOT/X-ray breast imaging system. Furthermore, the validation of the algorithm was provided using phatoms to systematically evaluate the impact of lesion sizes, contrasts and tissue background on the recovery of breast tumors.

The results show that, the tumor contrast metrics can find a region where the optical properties have a significant increase or decrease depending of the tumor type. Moreover, the optical properties to obtain reliable contrast metrics in a malignant lesion are the total hemoglobin concentration (HbT) and the reduced scattering coefficient ($\mu_s^{'}$), and for a benign lesion are HbT and the oxygen saturation (So_2).

In respect to the automatic tumor location and classification method, the retrieved information is capable of diagnosing the breast, as normal or not. In an abnormal case, our algorithm can potentially pinpoint the "suspicious" regions for the location of the tumor. The application of this method in the set of 126 breasts had a success rate of 82%. However, considering only the benign lesions was observed that in half of the sample, the algorithm failed.

These promising results could be used to provide more knowledge regarding the tumor location. Moreover, combining this results with further investigation and optimization they would be useful to achieve a tool that automatically gives precise "suspicious" regions for the tumor location to the doctor during the image reading.

KEYWORDS: Absorption | Diffuse Optical Tomography | Metrics | Scattering | Compositional-prior-guided reconstruction

RESUMO

O cancro consiste na proliferação anormal de células. No seu estado normal, as células crescem e dividem-se em novas células (regeneração celular). Quando estas envelhecem ou são danificadas, morrem naturalmente. No entanto, as células podem perder este mecanismo de controlo, tornando-se células cancerígenas, que produzem novas células de forma descontrolada, resultando na formação de um tumor. Os tumores podem ser benignos ou malignos. Apenas os tumores malignos são considerados cancro, sendo que as células podem invadir e danificar os tecidos e órgãos (metastização).

O cancro da mama é o tipo de cancro mais comum entre as mulheres (não considerando o cancro da pele) e corresponde à segunda causa de morte no Mundo e de acordo com o RON (Registo Oncológico Nacional), em Portugal, anualmente são detectados cerca de 4500 novos casos de cancro da mama, e 1500 mulheres morrem com esta doença. Desta forma, o diagnóstico precoce do cancro da mama é essencial, sendo que a mamografia convencional continua a ser a principal técnica de imagiologia utilizada para o efeito. No entanto, contribui para falsos negativos e não deteta cerca de 10-15% dos cancros da mama, principalmente em mulheres com mamas mais densas.

Tomografia ótica difusa (do inglês, *Diffuse Optical Tomography*, DOT) é uma técnica de imagiologia que permite obter imagens funcionais da mama. A técnica de tomografia ótica difusa é não-invasiva uma vez que utiliza luz na região espectral próxima do infravermelho (do inglês, *Near Infrared*, NIR), o que corresponde a comprimentos de onda entre aproximadamente 600 e 1000 nm. Nesta região espectral, a absorção da luz pelos tecidos é fraca e portanto a dispersão é maior em todas as direções, o que torna possível a detecção da luz emergente. Os principais absorvedores da luz na região próxima do infravermelho são: a oxi-hemoglobina (HbO) e a deoxi-hemoglobina (HbR), que contribuirão para o coeficiente de absorção medido (μ_a). O coeficiente de dispersão reduzido ($\mu_s^{'}$) irá depender do tecido mamário, já que está relacionado com a densidade e tamanho das partículas constituintes do meio. Com base nesses parâmetros, são obtidos mapas espaciais das propriedades óticas do tecido, tais como a concentração de hemoglobina total (HbT), a saturação de oxigénio (So_2) e o coeficiente reduzido de dispersão ($\mu_s^{'}$) através de algoritmos de reconstrução da imagem. Tais propriedades permitem inferir acerca da oxigenação e vascularização do tecido.

No entanto, as imagens de DOT apresentam baixa resolução espacial devido à extrema sensibilidade ao ruído durante o processo de recontrução da imagem. Para tal, tem sido alvo de muito investigação a incorporação de outras técnicas de imagiologia, especialmente as que fornecem informação estrutural. Nesse sentido, foi desenvolvido um sistema combinado de DOT e Raio-X no Massachusetts General Hospital (Boston, EUA) para o diagnóstico de cancro da mama. Sendo que, por um lado, é possível explorar a distribuição da absorção e dispersão da luz no tecido fisiológico e, por outro, adquirir informação de cariz anatómico.

Na maioria dos estudos de sistemas híbridos com DOT, as modalidades de imagiologia estruturais têm sido utilizadas apenas para fornecer o limite exterior da mama, ou então através da sobreposição nas imagens reconstruídas de DOT e posterior interpretação das imagens pelo médico/radiologista. No entanto, a estrutura anatómica interna é um fator chave que está em falta para produzir imagens com

melhor resolução espacial. Assim, de modo a incorporar este fator na recontrução das imagens de DOT, têm sido propostos e testados novos algoritmos.

Juntamente com outros grupos de investigação, Fang *et al.* desenvolveu o método de reconstrução *prior-guided*. Neste método é considerada uma segmentação composicional da mama e assume-se que cada pixel na imagem anatómica resulta da combinação de dois ou mais tipos de tecido. Estudos posteriores tem revelado que este método permite manter a resolução espacial das imagens anatómicas e, para além disso, tem mostrado ser robusto no processamento de imagens em meio clínico. Recentemente, um estudo realizado por Deng *et al.* revelou que esse método de reconstrução permite detectar quando a localização do tumor fornecida é falsa. Ou seja, apenas quando a localização do tumor fornecida é verdadeira, é que se observa uma diferença significativa no contraste óptico. Esse estudo serviu como motivação para a realização do trabalho descrito nesta tese.

A presente tese reflecte o trabalho realizado no *Athinoula A. Martinos Center for Biomedical Imaging*, parte do *Massachusetts General Hospital and Harvard Medical School* sob a orientação do Professor Qianqian Fang e ainda sob orientação do Professor Nuno Matela da Faculdade de Ciências da Universidade de Lisboa, Portugal - num período de estágio de duração de 8 meses, em Boston.

Até agora, a maioria dos estudos clínicos usando sistemas híbridos de imagem da mama com DOT têm-se concentrado em caracterizar apenas tumores conhecidos. Não tem sido demonstrado que os métodos de reconstrução de imagem DOT podem ser utilizados para identificar a localização e o tipo de lesão desconhecido. Desta forma, o objetivo principal desta tese consistiu no desenvolvimento de um método de detecção automático para identificar a localização e tipos de lesão sem a interferência de um radiologista.

A tese apresentada reflecte os métodos, resultados e conclusões de uma ferramenta de deteção automática que realça potenciais regiões para a localição e classificação do tumor. Esta ferramenta foi desenvolvida com base no desenvolvimento de múltiplas métricas de contraste. Para tal, recorreu-se em primeira análise, a dados provenientes de uma amostra de 126 mamas, dos quais 60 são consideradas mamas anormais (com tumor) e 66 normais (sem tumor). Posteriormente, utilizou-se modelos digitais da mama (fantomas) de modo a simular diferentes tamanhos e tipos de tumor. De modo geral, as etapas chave para o desenvolvimento deste trabalho foram as seguintes:

1. Implementação de uma grelha que define as localizações do tumor;
2. Desenvolvimento de múltiplas métricas para casos malignos, benignos e normais;
3. Verificação e validação das métricas utilizando dados provenientes de uma amostra de pacientes e de modelos digitais da mama;
4. As métricas de contraste foram combinadas de modo a localizar o tumor;
5. As métricas foram utilizadas para confirmar a natureza do tumor.

Os resultados obtidos mostraram que as métricas de contraste definidas, permitem identificar a região onde as propriedades ópticas têm uma alteração significativa de contraste e consequentemente permitem localizar o tumor. No entanto, esses resultados variam consoante a natureza do tumor. Assim,

lesões malignas causam um contraste positivo, contrariamente às lesões benignas, cujo contraste é negativo. As métricas de contraste designadas por M1, M2, 2 and M3 são eficazes para a localização de tumores malignos, enquanto que as métricas de contraste B1, 2 and B2 são eficazes para identificar a localização de tumores benignos. De modo a tornar a localização do tumor mais robusta, recorreu-se a análise de duas propriedades óticas, à concentração de hemoglobina total (HbT) e ao coeficiente de dispersão reduzido ($\mu_s^{'}$) para lesões malignas. Do mesmo modo para as lesões benignas, no entanto em vez do coeficiente de dispersão reduzido, considerou-se a saturação de oxigênio (So_2).

A partir da combinação de múltiplas métricas foi desenvolvida uma ferramenta que permite localizar e classificar o tumor. Este método permite classificar a mama como normal ou não. No caso de a mama ser classificada como anormal, o método aponta no mínimo duas regiões "suspeitas" para a localização do tumor dependendo da natureza do tumor. Assim, este método resulta numa imagem de raio-x com duas localizações: 1) região "suspeita" para tumor maligno; e 2) região "suspeita" para tumor benigno. A aplicação deste método na amostra de 126 mamas apresentou uma taxa de sucesso de cerca de 82%, porém considerando-se apenas as lesões benignas foi observado que em metade da amostra, o método falhou na localização do tumor. Uma das desvantagens deste método, é que a decisão final continua a ser dependente do doctor/radiologista.

Os resultados são de interesse para a comunidade científica, principalmente grupos de investigação na área de imagiologia ótica. Este estudo revela que recorrendo ao método de localização e classificação do tumor é possível localizar de modo preciso o tumor. Este método merece investigação futura, no que diz respeito à sua aplicação em meio clínico como o sistema de apoio computorizado ao diagnóstico (do inglês, *Computer Aided Detection*, CAD), permitindo auxiliar o médico/radiologista a detectar lesões durante a leitura da imagem.

Este trabalho poderá vir a encorajar estudos futuros de modo a otimizar o algoritmo. Para tal, é fundamental a análise da influência do tamanho do tumor e da fatia (do inglês, *slice*) da imagem reconstruída considerada; seria igualmente importante aumentar consideravelmente o número de pacientes em estudo, de forma a validar e metodologia implementada; e por fim, o desenvolvimento de um método capaz de distinguir um tumor benigno de um maligno seria um fator chave.

PALAVRAS-CHAVE: Absorção | Dispersão | Métricas | Reconstrução de Imagem | Tomografia Óptica Difusa

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NOMENCLATURE

Roman symbols

μ	Vertical vector recording the reconstructed functional values at all parameter nodes.
$\mathbf{C}(\mathbf{r})$	Compositional vector.
χ	Pixel intensity.
$b(r)$	Scattering power.
C_a	Composition of the adipose tissue.
C_f	Composition of the fibroglandular tissue.
f	Function.
I	Optical intensity of the transmitted light.
I_0	Optical intensity of the incident light.
I_s	Image intensity in the measured structural image.
r_0	Centroid of the tumor.
$S(r)$	Source.
$S_0(r)$	Phasor of the source.
w	Angular frequency.
x	Distance in the propagation direction of the sample or Vector of chromophore concentration.
A	Forward operator.
c	Speed of light in the medium.
D(r)	Diffusion coefficient.
G	Gaussian distribution.
I	Identity matrix .
J, H	Jacobian and Hessian matrix, respectively.

Greek symbols

χ^2	Quantifies the discrepancy between the calculated and measured data fluency rate.
λ	Wavelength or Tikhonov regularization parameter.
μ_a	Absorption Coefficient.
μ_s	Scattering Coefficient.
$\mu_s^{'}$	Reduced Scattering Coefficient.
$\phi(r)$	Fluency rate.
σ	Standard deviation of the Gaussian sphere
φ	Tumor size parameter or measurement data.
Υ	Contrast parameter.

Subscripts

a	Adipose tissue.
f	Fibroglandular tissue.
t	Tumor tissue

Superscripts

T	Transpose.

ACRONYMS

SO_2	Oxygen Saturation.
2-D	Two Dimensional.
3-D	Three Dimensional.
ACS	American Cancer Society.
CAD	Computer Aided Detection.
CDF	Cumulative Distribution Functions.
CT	Computed tomography.
CVD	Cardiovascular Diseases.
CW	Continuous-wave.
DBT	Digital Breast Tomosynthesis.
DCIS	Ductal Carcinoma In Situ.
DOT	Diffuse Optical Tomography.
FD	Frequency-domain.
FEM	Finite Element Method.
FWHM	Full-width Half-Maximum.
HBO	Oxygenated Hemoglobin.
HBR	Deoxygenated Hemoglobin.
HBT	Total Hemoglobin Concentration.
IARC	International Agency for Research on Cancer.
IDC	Invasive Ductal Carcinoma.
ILC	Invasive Lobular Carcinoma.
LCIS	Lobular Carcinoma In Situ.
MGH	Massachusetts General Hospital.
MRI	Magnetic resonance imaging.
MUX	Multiplexer Unit.
NIR	Near Infrared.
PET	Positron emission tomography.
RF	Radio Frequency.
RTE	Radiative tranfer equation.
SPECT	single photon emission computed tomography.

WHO World Health Organization.

1 INTRODUCTION

Since the first anatomical sketches of Leonardo da Vinci that human beings aspire to view the body structures as precisely as possible. Over the last century, imaging, joining scientific fields as physics, medical sciences and engineering, has provided a wide range of tools which contribute decisively to the understanding of the functioning of the human body and their constituents. Among other applications, these tools play an invaluable to non-invasive diagnosis, monitoring of diseases, as well as in the planning and evaluation of potential therapies.

In this chapter, the overall project motivation is described, the aims and objectives of the thesis are introduced, and finally the details of the structure of the present thesis are given.

1.1 CANCER IMAGING

Based on the definition given by the American Cancer Society (ACS), cancer is the term used to describe a condition which is characterized by a population of cells that grow and divide in an uncontrolled manner and which has the ability to invade and destroy surrounding tissues and also to spread throughout the body, leading to metastasis.

The rapid increase in the incidence of cancer is now a serious public health problem all over the world and is considered the second leading cause of death after cardiovascular diseases (CVD). According to demographic analysis of the International Agency for Research on Cancer (IARC) of the World Health Organization it is expected that the number of new cases of diagnosed cancer and registered deaths will double in the next two decades [1]. Cancer can develop almost anywhere in a human body, such as the skin, marrow, bone, brain, breast, colon, liver and lung. Whereas, breast cancer is the second cause of death from cancer between women [2].

The breast cancer tumors can be benign or malignant. Benign tumors are classified non-cancerous because they are not typically aggressive toward surrounding tissue, unlike malignant tumors that invade and damage surrounding tissue. Most of the breast tumors start in the duct and lobular tissues of the breast (Figure 1.1). Common benign breast tumors include fibrosis, the growth of scar-like tissue, and cysts, which are abnormal liquid-filled sacs. Ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) are considered pre-cancer because some cases can become invasive cancers (malignant tumors). The most common invasive breast cancers are invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). The IDC begins in the milk duct of the breast and grows into the surrounding normal tissue in the breast. ILC starts in the milk-producing glands (lobules) and like IDC, ILC spreads

to others parts of the body.

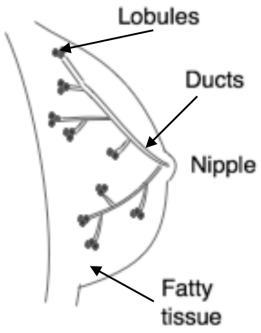

Figure 1.1: Healthy Breast Anatomy.

It has been reported that detection of breast cancer in early stages is essential for reducing the breast cancer mortality rate [3]. The standard mammography is focused on clinical diagnosis at an early stage of the disease and essentially provide anatomical information. However, only the detection of morphological changes in tissues have shown to be insufficient in several cases [1].

In recent years, a growing research interest is found for developing multi-modal imaging methods. This type of device usually combines, on the same physical system, the ability to acquire accurate anatomical images and the capability of obtaining functional images. Multi-modality systems are gradually closing the gap between the morphological changes and the metabolic processes in the tissue, becoming abundant in clinical practices.

Multi-modal diffuse optical tomography (DOT) is becoming increasingly popular among researchers. DOT images are intended to represent the functional processes in the tissue by utilizing light in the near-infrared spectral window of 600-1000nm, wherein light in tissue is dominated by scattering rather than absorption. Optical measurements at multiple source-detector positions on the tissue surfaces can be used to reconstruct the internal distribution of the absorption coefficient and the reduced scattering coefficient in three-dimensions (3D). Physiological images of total hemoglobin concentration (HbT), oxygen saturation (So_2) are then derived from this information. Thus, those parameters have shown to have a key role in clinical diagnosis of breast cancer [4]-[5]. For breast tumor diagnosis and screening, the literature have reported DOT combined with ultrasound by Zhu et al. [6] and with MRI by different groups of investigation like Ntziachristos et al. [7], Brooksby et al. [8] and Carpenter et al. [9]. Furthermore, a combined DOT and X-ray system was built at Massachusetts General Hospital [10, 11]. As regards the latter point, the X-ray is presented as the standard imaging technique, since achieves good anatomical information with high sensitivity [1] (spatial resolution) and, on the other hand, DOT is associated to high specificity [2] compared to the X-ray technique.

Merely as an example, some reconstructed optical and x-ray images are shown in Figure 1.2 from an abnormal breast for different optical properties explained in details in the next Chapter. Black arrows indicates the tumor region.

[1] Sensitivity measures the proportion of positives that are correctly identified as such (e.g., the percentage of sick people who are correctly identified as having the condition).

[2] Specificity measures the proportion of negatives that are correctly identified as such (e.g., the percentage of normal breast who are correctly identified as not having the condition).

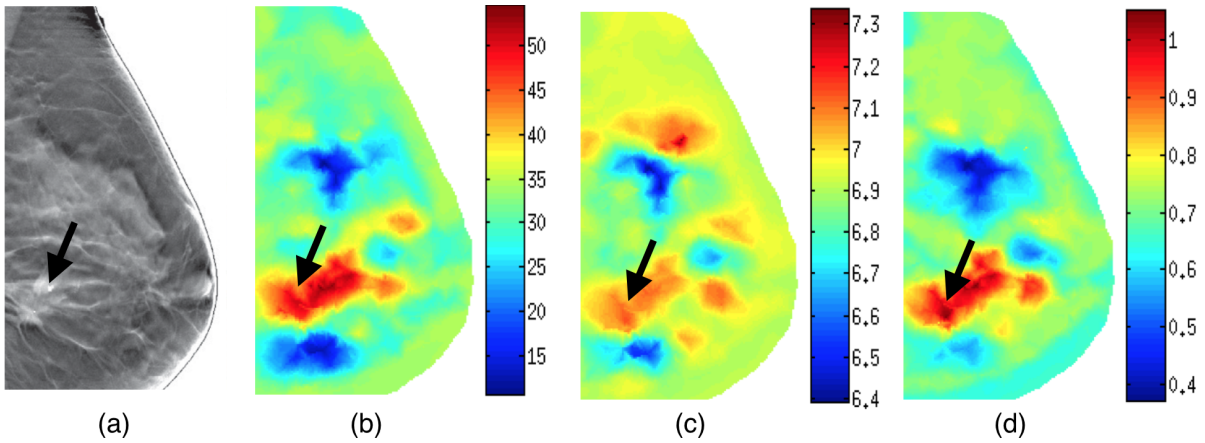

Figure 1.2: Reconstructed image sections. (a) X-ray image and (b) HbT (micromoles per liter), (c) So_2, and (d) $\mu_s^{'}$ (cm^{-1}) images at 830 nm. The breast contains a 2.5 cm invasive ductal carcinoma (arrow on a-d).

1.2 Motivation and Objectives

The medical imaging, in particular, multi-modality systems like DOT/DBT, is an area of research in development in recent years and one of the best examples of how engineering, physics and computer science can be used to benefit the medicine.

One of the physical phenomena associated with DOT is related to the diffusive nature that photons may suffer inside the tissue. This phenomenon causes low spatial resolution in the reconstructed images and thus the images obtained do not reflect the distribution of the optical properties. Of the various strategies developed to address this problem, the structural priors is the methodology that results in more accurate spatial details [12, 13].

Study reported by Deng *et al.* [13] indicates that by using the structural priors, the error of the optical property estimation can be reduced by 50% and is shown to be robust to false priors on tumor location. This fact deserves more exploration and further investigations. So far, most clinical research of either standalone or multi-modal DOT breast imaging system have been focusing on characterizing known tumors. It has not been shown that, DOT based imaging methods can be used to identify the location, and type of an unknown lesion. So, the key objective of this work is a computer aided detection (CAD) method to automatically identify the location and types of an unknown lesion without interference from a radiologist.

This study took place at Athinoula A. Martinos Center for Biomedical Imaging, part of Massachusetts General Hospital, more specifically at the optical division. They introduced the first DOT/X-ray combined system over 10 years ago [10]. Since then, several improvements in the device, algorithms of image reconstruction and clinical trials have been implemented.

1.3 Thesis Outline

This thesis is structured into seven chapters and four attachments. The thesis organization is schematically represented in Figure 1.3.

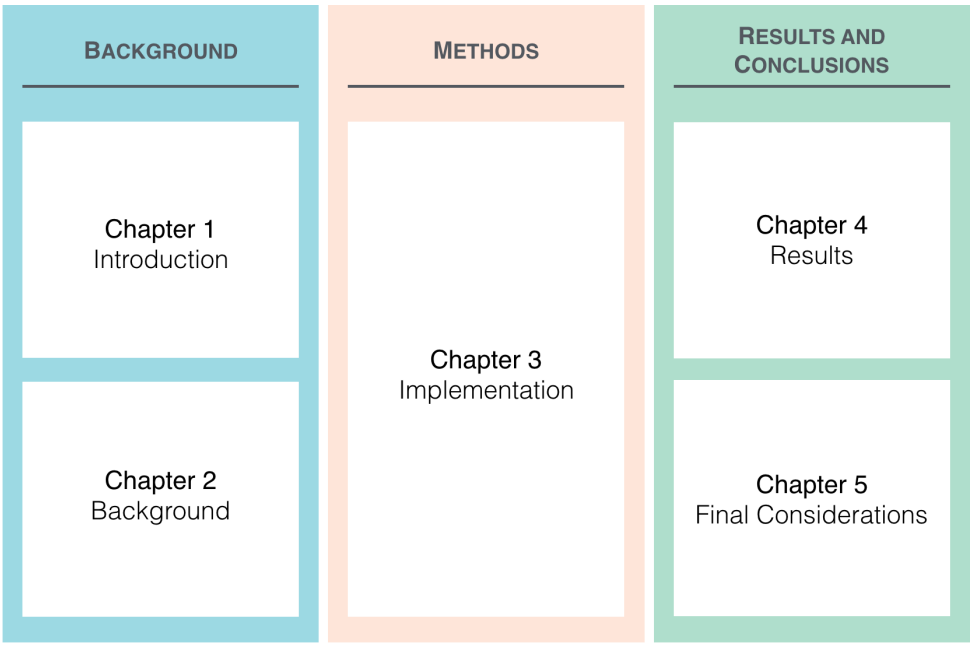

Figure 1.3: Representative diagram of the dissertation structure.

Chapter 1 introduces the subject in order to contextualize the reader with the project, stating the objectives, motivation and the importance of the work presented here. Chapters 2 focuses on the main theoretical concepts that support the thesis, providing a general approach to DOT, through the physical principles, characteristics of the equipment, the data acquisition and basis of optical tomographic image reconstruction. Chapter 3 presents the methodology proposed in this work, which is divided into four main sections: i) Compositional prior guided reconstruction: we describe the algorithm used to reconstruct the images ii) Contrast metrics: we define multiple contrast metrics for malignant, benign and normal cases; iii) Localization: We combine multiple metrics to robustly locate the tumor and, iv) Classification: we use the contrast metrics to confirm the nature of the tumor. The two chapters that follow are the designated block by results and final considerations. In Chapter 4 the experimental results are both listed and discussed. Finally, Chapter 5 presents the conclusions of this work, as well as some of the limitations and future prospects regarding the implementation of the algorithm proposed.

2 BACKGROUND

In this chapter some basic background information is provided. This chapter begins with a description of the optical properties of tissues. The origins of optical contrast in breast imaging are then detailed. Finally, we will focus on diffuse optical tomography (DOT) imaging and in the combined DOT/X-ray breast imaging system.

2.1 OPTICAL TOMOGRAPHY

Optical tomography is a novel medical imaging technique that uses near infrared (NIR) region of the electromagnetic spectrum (from about 600 nm to 1000 nm). NIR light has during recent years become a very attractive method for physiological analysis of tissue, since it can be applied in biological tissues non-invasively. As a result, many research studies have been reported to show its application for the diagnosis and screening of breast cancer [14, 15, 16, 17, 18] and monitoring treatments [19, 20].

2.1.1 OPTICAL PROPERTIES OF TISSUE

In the NIR spectral window, the interaction between the photon and the tissue can be primarily characterized by two effects: scattering and absorption. When the scattering effect of a medium is negligible, the light travels a straight path and the incident beam direction is attenuated as illustrated in Figure 2.1. The strength of the absorption effect is characterized by the absorption coefficient, μ_a (in cm^{-1}), and

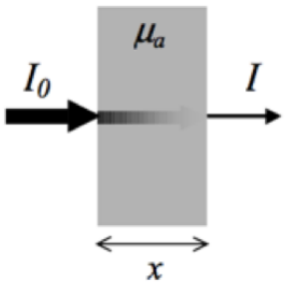

Figure 2.1: Attenuation of light through a non-scattering medium.

depends of the number of absorbing substances (chromophores). The extinction coefficient of each chromophore represents their absorption at a particular concentration. So, the absorption coefficient of a mixture of chromophores can be expressed as the sum of the products of the concentration of each

chromophore c_n with its extinction coefficient ε_n in the wavelength λ.

$$\mu_a(\lambda) = \sum_n \varepsilon_n(\lambda) c_n \tag{2.1}$$

However, when a medium has the scattering effect much greater than the absorption, the light can be scattered in different directions as illustrated in Figure 2.2. The scattering coefficient is quantified by μ_s (in cm^{-1}). In those cases, the medium is called dense and the light diffuses through the medium. For this reason, the name given to the study of light propagation in dense medium is called diffuse optics. Light propagation through scattering medium is described using the diffusion approximation

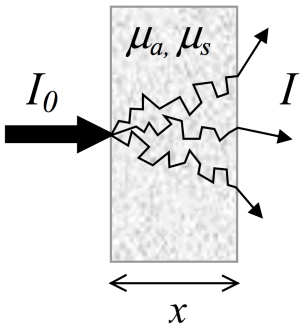

Figure 2.2: Attenuation of light through a scattering medium.

to the radiative transfer equation (RFE). In the NIR spectral window, the effect of scattering is often described in terms of the reduced scattering coefficient, ($\mu_s^{'}$ in cm^{-1}), that in tissue follows a simplified Mie-scattering approximation [21]:

$$\mu_s^{'}(\lambda, r) = A(r)\lambda^{-b(r)} \tag{2.2}$$

where $A(r)$ is the scattering amplitude of $\mu_s^{'}(\lambda)$, which scales the wavelength-dependent term and $b(r)$ is called the scattering power.

Analyzing the absorption spectrum plot in Figure 2.3, the primary absorbers of ligth in the NIR spectrum (600 to 1000 nm) are oxygenated hemoglobin (HbO) and deoxyhemoglobin (HbR), which will contribute to the measured absorption coefficient. Once chromophore concentrations are obtained (HbO and HbR), it is possible to determine the total hemoglobin concentration (HbT in μM) - Equation 2.3 - and the tissue blood oxygen saturation (So_2 in %) - Equation 2.4.

$$HbT = HbO + HbR \tag{2.3}$$

$$So_2 = HbO/HbT \tag{2.4}$$

The total hemoglobin concentration is the number of red blood cells in a unit volume of tissue (in microMolar). The red blood cells delivers oxygen to tissues by attaching to oxygen in the lungs and becoming oxy-hemoglobin (HbO). At the tissue, the oxygen dissociates to leave deoxy-hemoglobin (HbR). The relative concentrations of oxy- and deoxy- hemoglobin in the blood tells us how well oxygenated the blood is. The oxygenation of blood in tissues is related to the supply and flow of tissue blood, and the

demand and usage of oxygen in the tissue. Note that, an actively growing malignant tumor is known to have highly bifurcated and clustered blood vessels to help its fast growth, presenting much higher hemoglobin concentration than the surrounding normal tissues [23]. In the meantime, the growth of the tumor requires more oxygen due to the increased metabolic level, thus lowering blood oxygenation. Using these characteristics, clinicians can potentially gain more accurate diagnosis.

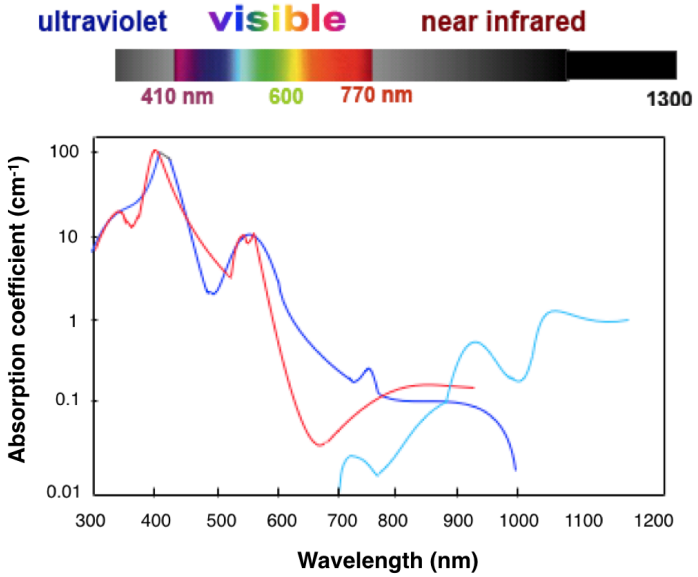

Figure 2.3: Absorption Spectrum: red, blue and baby blue represents HbO, HbR and water, respectively. (Adapted from [22])

2.1.2 Contrast in Breast Clinical Optical Imaging

Optical tomography has the potential to identify the nature of suspicious lesions in the breast during screening. In the normal breast, fibroglandular tissue has been found to be more scattering and absorbing than adipose tissue. As previously mentioned, breast tumor can be benign or malignant. The edges of the tumor are usually very distinct and demarcated in a certain shape. As a general rule, the malignant tumor may have an irregular shape and benign tumors are usually round. Depending of the tumor type, the optically detectable features change. These differences may be sufficient for diagnostic purposes as summarized in Table 2.1.

Condition	Type	Shape	Likely to manifest as
Cyst	Benign	Round and smooth	Low scatter
Blood filled cyst	Possible Malignant	Round and smooth	High absorption, possible low scatter
Fibroadenoma	Benign	Round and mobile	High scatter, possible high absorption, normal vasculature
Fibrocystic	Benign	Boundaries not discrete	High scatter
Dormant tumor	Malignant	Small, within ducts or lobes	Possible necrotic
Growing tumor	Malignant	Boundaries not discrete	Increased vasculature[1]

Table 2.1: Different malignant and benign lesions their potential optically detectable features.[1]Hence increased absorption, scatter and anomalous oxygenation. (Adapted from [16, 24, 25])

2.1.3 DIFFUSE OPTICAL TOMOGRAPHY (DOT)

The essence of DOT is based on the contrast caused by the optical properties of tissue, known as oxy- and deoxy- hemoglobin concentrations (HbO and HbR, respectively) and the scattering properties ($\mu_s^{'}$). The problem associated with this technique is the low spatial resolution of the DOT reconstructed images [26], that greatly limits its adoption in the clinic. By incorporating anatomical images to DOT modality, the barrier between the low resolution at DOT and the clinical practices was broken. In that sense, a dual-modality system with DOT and X-ray was developed at MGH for the screening and diagnosis of breast cancer.

In this thesis, we will focus on the combined DOT/X-ray breast imaging system. In the following subsections, we will discuss the fundamentals behind this technique, the key characteristics of data acquisition and reconstruction image. Finally, the algorithm of image reconstruction will be briefly presented.

2.2 X-RAY/OPTICAL BREAST IMAGING SYSTEM

As mentioned in the previous section, a combined X-ray/optical breast imaging is a system for acquisition of morphological and functional images of the breast, noninvasively. Generally a DOT/X-ray study includes the following three steps: i) acquisition and data logging; ii) image reconstruction; and iii) image analysis. It should be noted that the acquired data depend on both the optical properties of tissue as the limitations of the equipment, which can negatively influence the quality of the formed image and its interpretation.

Currently, the process of forming an image by DOT/X-ray requires off-line computation. Following the acquisition of data during the examination, it is necessary to process the data stored by means of algorithms reconstruction image in order to get as a final result, an image that reflects the contrast distribution of the optical properties in the tissue and allows inferences about the state of health of the anatomical structure under study. In this section we will discuss the data acquisition process and the image reconstruction.

2.2.1 DATA ACQUISITION

The Figure 2.4 illustrates a picture of the combined optical and X-ray imaging system developed at MGH. The X-ray unit is a tomosynthesis system [3] and the optical imaging system consists of light sources and optical detectors.

A schematic description of DOT is given in Figure 2.5. The aim is to reconstruct the internal distribution of optical properties within the breast by injecting light on the surface and detecting light that has propagated through the breast to another point on the surface. The algorithm for the image reconstruction will be described in the next sub-section.

[3] Tomosynthesis is a special kind of mammogram that produces a 3-dimensional image of the breast by using several low dose x-rays obtained at different angles.

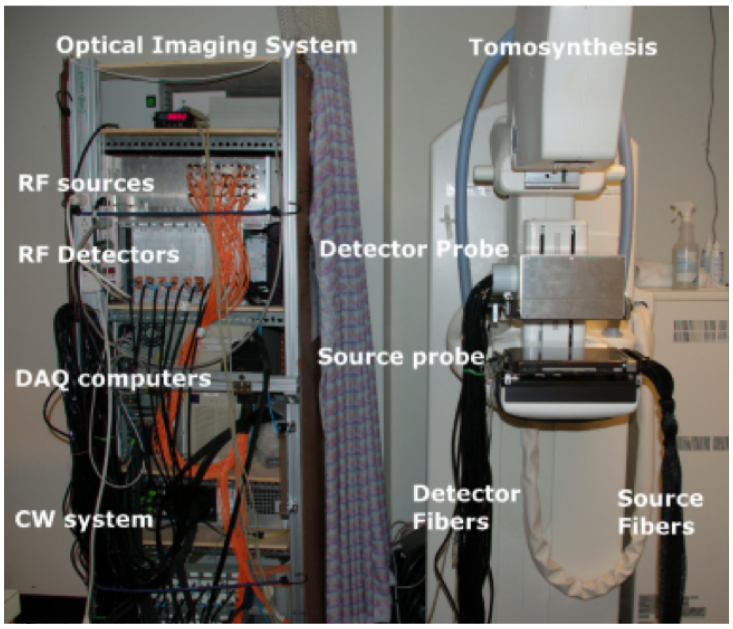

Figure 2.4: Picture of the combined DOT/x-ray system in clinical environment, including both RF and CW source/detector modules and the fiber optics interface attaching to the x-ray system. (Duplicated from [11])

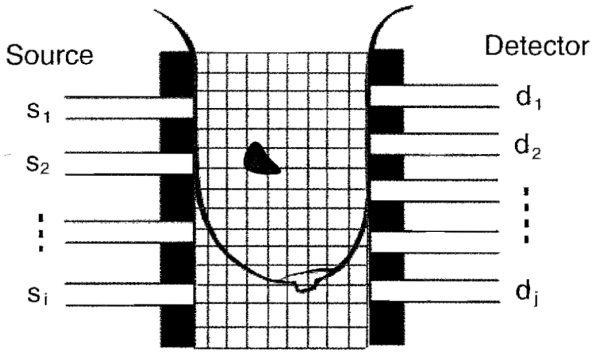

Figure 2.5: Schematic of diffuse optical tomography. A breast with tumor is placed between source and detector plate as shown. Measurements from different source-detector pairs on the surface of the breast enable reconstruction of the spatial distribution of internal optical properties. (Duplicated from [27])

The source generates the red and infrared light. In this system two types of measurements are used: a continuous-wave (CW) and a Frequency-domain (FD) system. Figure 2.6 schematically illustrates the input light source (solid line) and the output signal (dotted line) for each measurement type. CW measurements employ a light source whose intensity does not vary with time. The detector measures the transmitted intensity, which is affected by the breast. Frequency-domain measurements employ a light source that is amplitude modulated in the radio frequency (RF) range. The detector measures the amplitude of the transmitted diffuse photon density wave and its phase-shift relative to the input. As the system has both light sources, it needs to switch between them, a process that is called "multiplexing". The RF unit provides two laser wavelengths (685 and 830 nm) at 40 source location and the CW unit three wavelengths (685, 810, and 830 nm) at 26 source location. The conversion of the light signal into an electrical signal is done with avalanche photodiode detectors.

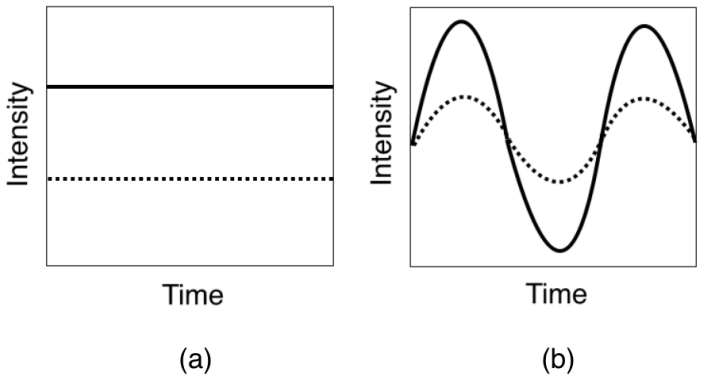

Figure 2.6: Measurements types: (a) Continuous-wave (CW); (b) Frequency-domain (FD) - solid line: input light source, dashed line: output detected signal.

The digital breast tomosynthesis system is a clinical prototype and it was developed by GE Healthcare. A schematic view of tomosynthesis acquisition is given in Figure 2.7. In breast tomosynthesis, the x-ray tube is moved through a limited arc angle while the breast is compressed. A series of exposures results in multiple projection image data sets. Each exposure is a fraction of the total dose used during conventional digital mammography. The sytem used has the capability of collecting 15 projections within a 45^{o} swing angle [28, 29].

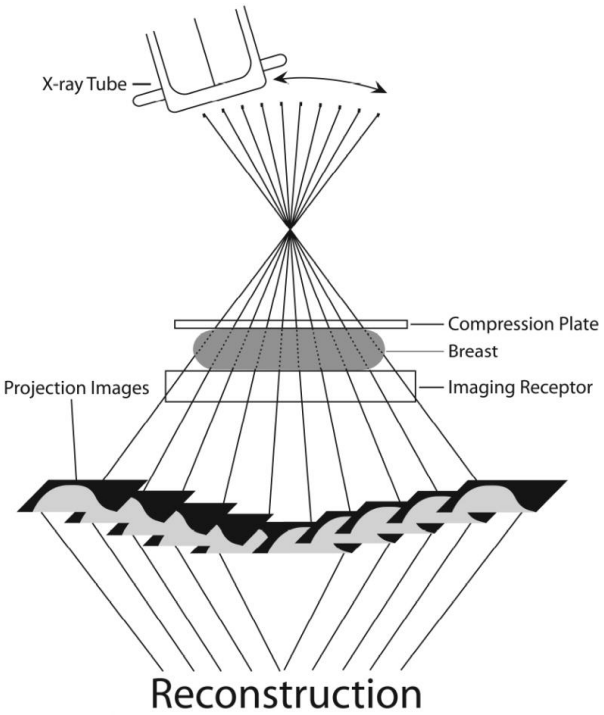

Figure 2.7: Schematic view of digital breast tomosynthesis. (Duplicated from [30])

2.2.2 IMAGE RECONSTRUCTION ALGORITHM

In digital breast tomosynthesis, the projection image data sets are reconstructed into multiple thin slice images (1 mm thickness) for interpretation by the radiologist. An iterative maximum likelihood algorithm

(described in [29]) is used to synthesize the two-dimensional projections into volumetric x-ray images, which have a voxel size of 0.1 mm in the x- and y-axes and 1 mm in the z-axis [28, 29]. The image reconstruction in DOT is an inverse problem. The optical parameters inside an unknown structure need to be estimated, the input is the light illumination and the output is the observed light distribution on the surface of the structure. A clinician often wants to have a quantitative measure of the optical parameters. Hereupon, the forward problem evaluates the output of the light distribution, having regard to a specific input.

A generalized outline of iterative model-based optical properties reconstruction is described in the flow chart in Figure 2.8.

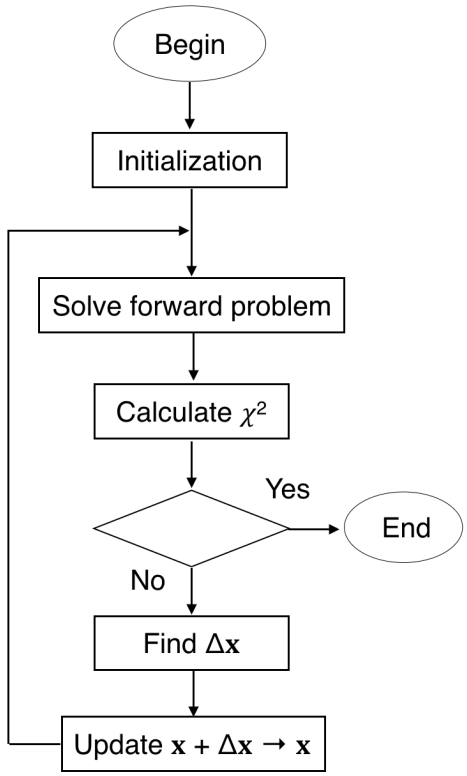

Figure 2.8: General analysis flow chart for iterative model-based optical properties reconstruction. (Adapted from [27])

Here x is a vector of unknown properties (HbR, HbO, constants A and b) for each node. The initialization process consists of reading in the measurement data, defining the reconstruction space, and assigning initial guess for $x(r)$, where r denotes position within the sample volume. The forward problem computes the fluency rate, $\phi(r)$, on the sample surface given light source information and optical property distribution $x(r)$. χ^2 quantifies the discrepancy between the calculated and measured data fluency rate; its value determines whether to update $x(r)$ and integrate again or to stop the calculation. If the stopping criteria are not met, the inverse problem estimates a change in optical properties, Δx, based on χ^2 for the next iteration. For the inverse problem, the reconstruction volume is discretized into nodes and the optical properties of each node are the unknowns to be reconstructed.

2.3 COMPOSITIONAL-PRIOR-GUIDED IMAGE RECONSTRUCTION ALGORITHM

As referenced in the Section 2.1, the spatial resolution of DOT images is recovered by incorporating anatomical imaging modalities. In early studies, the structural information was used to delineate the boundaries of the breast or for the image interpretation by overlaying in the DOT images. In recent years, considerable researchs in combining the structural and functional information simultaneously can be found. Brooksby et al. [8, 31] developed the "hard prior" method, in which the structural image is segmented and the nodes inside of each segment are characterized by the same optical parameters. To simultaneously consider the optical measurements and the structural information, "soft priors" based regularization methods have been applied by Li et al. [32], Brooksby et al. [31] and Yalavarthy et al.[33].

In order to consider the breast as a combination of different types of tissues, Fang et al. [12] have developed the compositional-prior-guided reconstruction algorithm. In this method, the nodes of the image are represented by the probability of each tissue type and they are assumed as a mixure of the contrast from each component, proportional to its concentration. So, the compositional vector at a given location r in the breast is given by

$$C(r) = \{C_i\}, i = 1, 2, ..., N_c \tag{2.5}$$

where $C_i(r)$ corresponds to the concentration ($0 \leq C_i(r) \leq 1$) of the i-th component at location r, and N_c is the total number of components. By definition, this equation also implies $\sum_i C_i(r) = 1$. This reconstruction method is the foundation for the work realized in this thesis and will be described in more details in the next chapter.

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